

1457327

## PATENT SPECIFICATION

(11) 1457327

(21) Application No. 20837/74 (22) Filed 10 May 1974  
 (61) Patent of addition to No. 1367550 dated 3 Oct. 1972  
 (31) Convention Application No. 359486 (32) Filed 11 May 1973 in  
 (33) United States of America (US)  
 (44) Complete Specification published 1 Dec. 1976  
 (51) INT CL<sup>2</sup> A61K 31/185  
 (52) Index at acceptance

A5B 281 28Y 380 382 383 386 38Y 392 396 39X 403 405  
 40Y 410 411 41Y 420 421 422 426 42Y 482 483  
 48Y 595 59Y

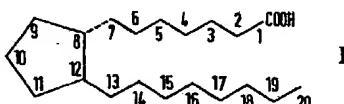
(72) Inventors RANDALL GEMMER STEHLE and  
 THOMAS OVID OESTERLING



## (54) PROSTAGLANDIN COMPOSITIONS

(71) We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, 5 Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described 10 in and by the following statement:—

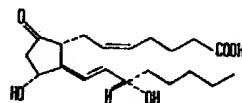
Prostanoic acid has the following structure and atom numbering:



15 Prostaglandins are related structurally to prostanoic acid, and prostaglandins of the E-type (PGE-type) all have the following structural feature:



20 For example, the prostaglandin known as prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) has the formula:



Other well known prostaglandins of the E-type are PGE<sub>1</sub>, PGE<sub>3</sub>, and 13,14 - dihydro - 25 PGE<sub>1</sub>. Esters of prostaglandins of the E-type are also known in the art. See, for example, British Patent Specifications Nos. 851,827 and 1,040,544.

As is known in the art, prostaglandins of

the E-type and their esters are extremely potent in causing various biological responses. For that reason, these compounds are useful for pharmacological and pharmaceutical purposes. See, for example, Bergstrom et al., Pharmacol. Rev. 20, 1 (1968), and references cited therein. A few of those biological responses are systemic blood pressure lowering as measured, for example, in anaesthetized (pentobarbital sodium) pentolinium - treated rats with indwelling aortic and right heart cannulas; stimulation of smooth muscle as shown, for example, by tests on strips of guinea pig ileum, rabbit duodenum, or gerbil colon; potentiation of other smooth muscle stimulants; antilipolytic activity as shown by antagonism of epinephrine - induced mobilization of free fatty acids or inhibition of the spontaneous release of glycerol from isolated rat fat pads; inhibition of gastric secretion as shown in dogs with secretion stimulated by food or histamine infusion; activity on the central nervous system; controlling spasm and facilitating breathing in asthmatic conditions; and decreasing blood platelet adhesiveness as shown by platelet-to-glass adhesiveness, and inhibition of blood platelet aggregation and thrombus formation induced by various physical stimuli, e.g., arterial injury, and various biochemical stimuli, e.g., ADP, ATP, serotonin, thrombin, and collagen.

Because of these biological responses, these known prostaglandins of the E-type and their esters are useful to study, prevent, control, or alleviate a wide variety of diseases and undesirable physiological conditions in birds and mammals, including humans, useful domestic animals, pets, and zoological specimens, and in laboratory animals, for example, mice, rats, rabbits, and monkeys.

For example, these E-type prostaglandins are useful in mammals, including man, as nasal decongestants. For this purpose, the compounds are used in a dose range of 10 µg. to 10 mg. per ml. of a pharmacologically suit-

30

35

40

45

50

55

60

65

70

able liquid vehicle or as an aerosol spray, both for topical application.

The E-type prostaglandins are useful in the treatment of asthma. For example, these compounds are useful as bronchodilators or as inhibitors of mediators, such as SRS-A, and histamine which are released from cells activated by an antigen - antibody complex. Thus, these compounds control spasm and facilitate breathing in conditions such as bronchial asthma, bronchitis, bronchiectasis, pneumonia and emphysema. For these purposes, these compounds are administered in a variety of dosage forms, e.g., orally in the form of tablets, capsules, or liquids; rectally in the form of suppositories; parenterally, subcutaneously, or intramuscularly, with intravenous administration being preferred in emergency situations; by inhalation in the form of aerosols or solutions for nebulizers; or by insufflation in the form of powder. Doses in the range of 0.01 to 5 mg. per kg. of body weight are used 1 to 4 times a day, the exact dose depending on the age, weight, and condition of the patient and on the frequency and route of administration. For the above use these prostaglandins can be combined advantageously with other anti-asthmatic agents, such as sympathomimetics (e.g. isoproterenol, phenylephrine and ephedrine); xanthine derivatives (theophylline and aminophylline); and corticosteroids (ACTH and prednisolone). Regarding the use of these compounds, see British Patent Specification No. 1,213,015.

The E-type prostaglandins are useful in mammals, including man and certain useful animals, e.g., dogs and pigs, to reduce and control excessive gastric secretion, thereby reducing or avoiding gastrointestinal ulcer formation, and accelerating the healing of such ulcers already present in the gastrointestinal tract. For this purpose, the compounds are injected or infused intravenously, subcutaneously, or intramuscularly in an infusion dose range 0.1  $\mu$ g. to 500  $\mu$ g. per kg. of body weight per minute, or in a total daily dose by injection or infusion in the range 0.1 to 20 mg. per kg. of body weight per day, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

The E-type prostaglandins are useful whenever it is desired to inhibit platelet aggregation, to reduce the adhesive character of platelets, and to remove or prevent the formation of thrombi in mammals, including man, rabbits, and rats. For example, these compounds are useful in the treatment and prevention of myocardial infarcts, to treat and prevent post-operative thrombosis, to promote patency of vascular grafts following surgery, and to treat conditions such as atherosclerosis, arteriosclerosis, blood clotting defects due to lipaemia, and other clinical conditions in which the underlying etiology is associated with lipid imbalance or hyperlipidaemia. For these purposes, these compounds are administered systemically, e.g., intravenously, subcutaneously, intramuscularly, and in the form of sterile implants for prolonged action. For rapid response, especially in emergency situations, the intravenous route of administration is preferred. Doses in the range 0.005 to 20 mg. per kg. of body weight per day are used, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

The E-type prostaglandins are especially useful as additives to blood, blood products, blood substitutes, and other fluids which are used in artificial extracorporeal circulation and perfusion of isolated body portions, e.g., limbs and organs, whether attached to the original body, detached and being preserved or prepared for transplant, or attached to a new body. During these circulations and perfusions, aggregated platelets tend to block the blood vessels and portions of the circulation apparatus. This blocking is avoided by the presence of these compounds. For this purpose, the compound is added gradually or in single or multiple portions to the circulating blood, to the blood of the donor animal, to the perfused body portion, attached or detached, to the recipient, or to two or all of those at a total steady state dose of 0.001 to 10 mg. per litre of circulating fluid. It is especially useful to use these compounds in laboratory animals, e.g., cats, dogs, rabbits, monkeys, and rats, for these purposes in order to develop new methods and techniques for organ and limb transplants.

The E-type prostaglandins are extremely potent in causing stimulation of smooth muscle, and are also highly active in potentiating other known smooth muscle stimulators, for example, oxytocic agents, e.g., oxytocin, and the various ergot alkaloids including derivatives and analogs thereof. Therefore, PGE<sub>2</sub>, for example, is useful in place of or in combination with less than usual amounts of these known smooth muscle stimulators, for example, to relieve the symptoms of paralytic ileus, or to control or prevent atomic uterine bleeding after abortion or delivery, to aid in expulsion of the placenta, and during the puerperium. For the latter purpose, the E-type prostaglandin is administered by intravenous infusion immediately after abortion or delivery at a dose in the range 0.01 to 50  $\mu$ g. per kg. of body weight per minute until the desired effect is obtained. Subsequent doses are given by intravenous, subcutaneous, or intramuscular injection or infusion during puerperium in the range 0.01 to 2 mg. per kg. of body weight per day, the exact dose depending on the age, weight, and condition of the patient or animal.

The E-type prostaglandins are useful as hypotensive agents to reduce blood pressure in mammals, including man. For this purpose,

the compounds are administered by intravenous infusion at the rate of 0.01 to 50  $\mu\text{g}$ . per kg. of body weight per minute or in single or multiple doses of 25 to 500  $\mu\text{g}$ . per kg. of body weight total per day.

The E-type prostaglandins are useful in place of oxytocin to induce labour in pregnant female animals, including man, cows, sheep, and pigs, at or near term, or in pregnant animals with intrauterine death of the foetus from 20 weeks to term. For this purpose, the compound is infused intravenously at a dose of 0.01 to 50  $\mu\text{g}$ . per kg. of body weight per minute until or near the termination of the second stage of labour, i.e., expulsion of the foetus. These compounds are especially useful when the female is one or more weeks post-mature and natural labour has not started, or 12 to 60 hours after the membranes have ruptured and natural labour has not yet started. An alternative route of administration is oral.

The E-type prostaglandins are useful for controlling the reproductive cycle in ovulating female mammals, including humans and animals such as monkeys, rats, rabbits, dogs and cattle. By the term ovulating female mammals is meant animals which are mature enough to ovulate but not so old that regular ovulation has ceased. For that purpose, PGE<sub>2</sub>, for example, is administered systemically at a dose level in the range 0.001 mg. to 2 mg. per kg. of body weight of the female mammal, advantageously during a span of time starting approximately at the time of ovulation and ending approximately at the time of menses or just prior to menses. Intravaginal and intrauterine are alternative routes of administration. Additionally, expulsion of an embryo or a foetus is accomplished by similar administration of the compound during the first third of the normal mammalian gestation period.

The E-type prostaglandins are useful in causing cervical dilation in pregnant and non-pregnant female mammals for purposes of gynaecology and obstetrics. In labour induction and in clinical abortion produced by these compounds, cervical dilation is also observed. In cases of infertility, cervical dilation produced by PGE and JGF compounds is useful in assisting sperm movement to the uterus. Cervical dilation by prostaglandins is also useful in operative gynaecology such as D and C (Cervical Dilation and Uterine Curettage) where mechanical dilation may cause perforation of the uterus, cervical tears, or infections. It is also useful in diagnostic procedures where dilation is necessary for tissue examination. For these purposes, the PGE-type compounds are administered locally or systemically. PGE<sub>2</sub>, for example, is administered orally or vaginally at doses of 5 to 50 mg. per treatment of an adult female human, with from one to five treatments per 24 hour period. PGE<sub>2</sub> is also administered intra-

muscularly or subcutaneously at doses of one to 25 mg. per treatment. The exact dosages for these purposes depend on the age, weight, and condition of the patient or animal.

As mentioned above, the E-type prostaglandins are potent antagonists of epinephrine-induced mobilization of free fatty acids. For this reason, this compound is useful in experimental medicine for both *in vitro* and *in vivo* studies in mammals, including man, rabbits, and rats, intended to lead to the understanding, prevention, symptom alleviation, and cure of diseases involving abnormal lipid mobilization and high free fatty acid levels, e.g., diabetes mellitus, vascular diseases, and hyperthyroidism.

Many prostaglandins of the PGE-type are also known in the art. All of these have the same cyclopentane ring structural feature of formula II, above, but differ from the prostaglandins of the E-type in one or more other structural aspects, for example, in having one or more substituents, for example, alkyl, fluoro, phenyl, or cycloalkyl, on either or both side chains, in having fewer or more methylene groups in one or both of the side chains, in having a hetero atom, for example, oxygen in place of a side-chain methylene group, in having a *cis* rather than a *trans* or a *trans* rather than a *cis* configuration for a side-chain carbon-carbon double bond, or in any combination of those structural aspects. Particularly important examples of E-type prostaglandins are PGE<sub>1</sub>, 15 - methyl - PGE<sub>1</sub>, 15 $\beta$  - 15 - methyl - PGE<sub>1</sub>, 15 - methyl - PGE<sub>2</sub>, 15 $\beta$  - 15 - methyl - PGE<sub>2</sub>, 16,16 - dimethyl - PGE<sub>1</sub>, 16,16 - dimethyl - PGE<sub>2</sub>, and 17 - phenyl - 18,19,20 - trinor - PGE<sub>2</sub>, and their methyl esters. Other examples of PGE-type compounds are 3 - oxa - PGE<sub>1</sub>, 3 - oxa - PGE<sub>2</sub>, 7 - oxa - PGE<sub>1</sub>, 17 - phenyl - 18,19,20 - trinor - PGE<sub>2</sub>, PGB<sub>1</sub>, 15 - methyl ether, PGE<sub>2</sub> 15 - methyl ether, 5,6 - trans - PGE<sub>2</sub>, 20 - ethyl - PGE<sub>2</sub>, 20 - methyl - PGE<sub>1</sub>, and 16 - fluoro - PGE<sub>2</sub>, and their esters. Such E-type prostaglandins and others of the E-type, are disclosed in, for example, British Patent Specifications Nos. 1,269,656; 1,282,661; 1,269,657; 1,299,136; 1,302,349; 1,314,291; 1,324,737; 1,331,826; 1,343,014; 1,350,971; 1,382,851; 1,392,991; 1,398,291 and 1,398,838; in German Offenlegungsschrift No. 2,150,361; French patent Specification No. 2,119,855; and in Belgian patent Specification No. 779,898.

The above-described structural variants of the E-type prostaglandins are useful for the same purposes described above for the E-type prostaglandins, and are used for those purposes in the ways described above.

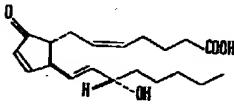
For the purposes of this invention, the term "prostaglandins of the E-type" includes both prostaglandins of the E-type, namely PGE<sub>1</sub>, PGE<sub>2</sub>, PGE<sub>3</sub>, dihydro - PGE<sub>1</sub>, and their esters, and also other carboxylic acid esters thereof

of the type exemplified above, namely those which are structurally similar to the E-type prostaglandins, having a cyclopentane moiety of formula II but with structural variations in either or both side chains, and causing at least part of the biological responses caused by E-type prostaglandins.

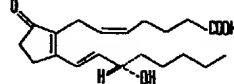
Also for the purposes of this invention, the term "prostaglandins of the E-type" is intended to include optically active compounds with the same absolute configuration as optically active PGE<sub>1</sub> obtained from certain mammalian tissues, for example, sheep vesicular glands or human seminal plasma. See, for example, Bergström et al., J. Biol. Chem. 238, 3555 (1963). This term is also intended to include racemic compounds but not the enantiomers of said optically active compounds. Thus, for example, the compound designated PGE<sub>2</sub> means an optically active compound with the natural configuration, and the corresponding racemate, and the compound designated 15 - methyl - PGE<sub>2</sub> means an optically active compound with the absolute configuration of PGE<sub>1</sub>, and also the corresponding racemate.

Also for the purposes of this invention, the term "prostaglandins of the E-type" is intended to include not only the carboxylic acids but also the esters of said carboxylic acids. Typical esters are those wherein the esterifying radical is alkyl of one to 12 carbon atoms, cycloalkyl of 3 to 10 carbon atoms, aralkyl of 7 to 12 carbon atoms, phenyl or phenyl substituted one to 3 times by chlorine atoms or alkyl radicals of one to 4 carbon atoms. Especially useful for the above described purposes are alkyl esters of one to four carbon atoms, and more especially methyl and ethyl esters.

One problem that has been observed in using and formulating PGE<sub>2</sub> is the stability of the compound. It tends to decompose, especially at room temperatures i.e. about 25°C., and higher, and especially in the presence of small amount of acid or base. In particular, in the presence of acid, PGE<sub>2</sub>, for example, changes to PGA<sub>2</sub> which has the formula:

50 

In the presence of base, PGE<sub>2</sub> changes to PGB<sub>2</sub> which has the formula:

55 

Similarly, the other prostaglandins of the E-type change to the corresponding compounds

of the A-type or the B-type. Even in neutral solution or in the solid state, there is a gradual change of E-types to A-types and B-types.

Reasonable stability of prostaglandins of the E-type has been observed in some solutions or in solid form when those are maintained at very low temperatures, for example, at -20°C. or lower. However, storage under such temperature conditions is usually inconvenient when the compounds are being used for the above-described purposes.

We described in our Application No. 45584/72 (Serial No. 1,367,550) that solutions of PGE<sub>1</sub> itself and racemates thereof in an anhydrous, water immiscible dipolar aprotic solvent have increased stability. We have now discovered that solutions of other prostaglandins of the PGE-type, (in addition to PGE<sub>2</sub>), in a concentration of at least 1 mg. per ml. of an anhydrous (as hereinafter defined), water-miscible, pharmacologically-acceptable, dipolar aprotic solvent also have surprisingly and unexpectedly increased stability even at room temperature i.e. about 25°C., and above. Stock solutions of the E-type prostaglandins so prepared, i.e., in an anhydrous, water-miscible, pharmacologically-acceptable, dipolar aprotic solvent, for example, anhydrous N,N - dimethylacetamide, can be stored at such temperatures for relatively long periods of time, for example, up to a year or more depending on the particular solvent and its water content, without excessive decomposition. Such solutions, therefore, provide a satisfactory method for storing the prostaglandin E-type compounds. Such solutions also provide a satisfactory method for dispensing the prostaglandin E-type compounds. For example, such a solution is packaged in unit dose containers, and when used, the contents of a container are diluted into a liquid or solid carrier for administration of a therapeutic dose. For example, the solution is diluted into water for enteral administration or into lactose tablets or a suppository base for intravaginal or rectal administration. When parenteral administration of the prostaglandin E-type compound is intended, such solutions are dispensed by sterilizing the solution, for example, by filter sterilization, and then aseptically packaging the solution in sterile containers in unit doses, diluting the contents of a sterile container with a sterile miscible diluent, for example, water, or isotonic saline or glucose solution, and then administering the diluted solution at a rate to administer a therapeutic dose.

While anhydrous N,N - dimethylacetamide is given by way of illustration, it is to be understood that other pharmacologically-acceptable, dipolar aprotic solvents can be used. Other suitable dipolar aprotic solvents include tetramethylurea, hexamethylphosphoramide, dimethylsulfoxide, sulfolane, acetone and isopropyl methyl ketone. The dipolar

aprotic solvents, especially N,N - dimethylacetamide, have great solvent power for prostaglandin-like E-type prostaglandins, and, moreover, give very stable solutions.

By water-miscible is intended those solvents which mix with water in all proportions or which are so highly soluble in water that they behave as if they were completely miscible.

It is desirable that the solutions according to the invention be relatively concentrated, i.e., concentrated relative to the effective concentration, i.e., the concentration at which the drug is used. Thus with N,N - dimethylacetamide or dimethylsulfoxide, or like dipolar aprotic solvent, the concentration could be as high as 100 mg./ml. or so. Ordinarily it will be sufficient if the solute is present in at least about 1 mg. per ml. Such solutions, though seemingly dilute, are relatively quite concentrated with respect to the effective concentration.

It is to be understood that pharmacologically-acceptable is to be based on the liquid or solid vehicle rather than on the stock solution. Some anhydrous solvents, for example, might not be pharmacologically-acceptable undiluted as in the stock solution but are very much so when diluted with a large volume of water as in enteral or parenteral administration or when diluted into a lactose tablet or suppository base for intravaginal or rectal administration. For example, 1 ml. of a 50 mg./ml. solution of PGE<sub>1</sub>, for example, diluted into 1 litre of infusion solution gives a solution containing 0.005% by weight of PGE<sub>1</sub>. At the same time the concentration of the solvent, 0.1% v/v, is well below that safe for intravenous infusion. Thus a pharmacologically-acceptable solvent as used herein is one which on dilution into the liquid or solid vehicle causes no untoward pharmacodynamic effect.

An anhydrous solution is to be considered as one containing not more than 0.5% v/v of water. All commercially available solvents contain water. Ordinary "pure" N,N - dimethylacetamide, for example, may contain up to 0.5% v/v water whereas "spectrograde" N,N - dimethylacetamide may contain as little as 0.03% v/v water. An anhydrous solvent, therefore, is to be considered as one containing not more than 0.5% v/v water. The Karl Fischer method can be used to determine the water content. It is actually preferred that the solvent, for example, N,N - dimethylacetamide, contains not more than 0.1% v/v water.

The invention will now be illustrated by the following Examples, in which the parts and percentages are by weight and the units in the C.G.S. system unless otherwise specified. Although all of these examples relate to PGE<sub>1</sub> and N,N - dimethylacetamide, it is to be understood that other prostaglandin-like E-type compounds in both free acid form and

ester form within the above-defined scope of this invention, including the compounds specifically named hereinabove, are transformed into stable solutions adapted for dispensing as set forth hereinabove, and that other anhydrous, water-miscible, pharmaceutically-acceptable, dipolar aprotic solvents than N,N - dimethylacetamide are also used for that purpose.

#### EXAMPLE 1

Parenteral grade PGE<sub>1</sub> is dissolved in anhydrous N,N - dimethylacetamide containing 0.4% v/v water (determined by the Karl Fischer method) in the proportions of 5 mg. PGE<sub>1</sub> for each ml. of anhydrous N,N - dimethylacetamide. The solution is then filter sterilized by passing it through a micro-porous (solvent-resistant) filter, e.g., Millipore (registered Trade Mark) Solvinert 0.25 microns or Gelman Metrical Alpha-8, 0.2 microns, aseptically packaged in 1 ml. quantities in sterile ampoules and kept under refrigeration at not more than 5°C. until needed. At that time the contents of one ampoule (1 ml.) are diluted into 1 L of infusion solution and administered intravenously at the rate of 5 mcg. of PGE<sub>1</sub> per minute.

#### EXAMPLE 2

Parenteral grade PGE<sub>1</sub> is dissolved in spectrograde N,N - dimethylacetamide (0.1% v/v water) in a concentration of 10 mg. per ml. The solution is filter sterilized as in Example 1 and packaged aseptically in 0.5 ml. quantities in sterile ampoules. This solution can be stored at room temperature.

#### EXAMPLE 3

Parenteral grade PGE<sub>1</sub> is dissolved in anhydrous N,N - dimethylacetamide (0.1% v/v water) in the proportions of 0.75 mg. PGE<sub>1</sub> to 1.5 ml. anhydrous N,N - dimethylacetamide. The solution is then filter sterilized as in Example 1, aseptically packaged in 1.5 ml. quantities in sterile ampoules, and kept under refrigeration at not more than 5°C. until needed. It is administered by diluting the contents of 1 ampoule (1.5 ml.) into 150 ml. of infusion solution and administered intravenously at the rate of 0.5 mcg. of PGE<sub>1</sub> per minute.

#### WHAT WE CLAIM IS:—

1. A solution of a prostaglandin of the PGE-type (other than PGE<sub>2</sub> itself or a racemate thereof) in an anhydrous (as hereinbefore defined), water-miscible, pharmaceutically-acceptable, dipolar aprotic solvent in a concentration of at least 1 mg. per ml.

2. A solution according to claim 1 wherein the prostaglandin is PGE<sub>1</sub> or PGE<sub>1</sub> methyl ester.

3. A solution according to claim 1 wherein

70

80

85

90

95

100

105

110

115

120

125

the prostaglandin is 15 - methyl - PGE<sub>1</sub> or 15 - methyl - PGE<sub>1</sub> methyl ester.

4. A solution according to claim 1 wherein the prostaglandin is 15 - methyl - PGE<sub>2</sub> or 15 - methyl - PGE<sub>2</sub> methyl ester.

5. A solution according to claim 1 wherein the prostaglandin is 15 $\beta$  - 15 - methyl - PGE<sub>1</sub> or 15 $\beta$  - 15 - methyl - PGE<sub>1</sub> methyl ester.

6. A solution according to claim 1 wherein the prostaglandin is 15 $\beta$  - 15 - methyl - PGE<sub>2</sub> or 15 $\beta$  - 15 - methyl - PGE<sub>2</sub> methyl ester.

7. A solution according to claim 1 wherein the prostaglandin is 16,16 - dimethyl - PGE<sub>1</sub> or 16,16 - dimethyl - PGE<sub>1</sub> methyl ester.

8. A solution according to claim 1 wherein the prostaglandin is 16,16 - dimethyl - PGE<sub>2</sub> or 16,16 - dimethyl - PGE<sub>2</sub> methyl ester.

9. A solution according to claim 1 wherein the prostaglandin is 17 - phenyl - 18,19,20 - trinor - PGE<sub>2</sub> or 17 - phenyl - 18,19,20 - trinor - PGE<sub>2</sub> methyl ester.

10. A solution according to any preceding claim which is sterile.

11. A solution according to any preceding claim in which the solvent is N,N - dimethylacetamide.

12. A solution according to claim 1 substantially as herein described.

For the Applicants,  
GILL, JENNINGS & EVERY,  
Chartered Patent Agents,  
51/52 Chancery Lane,  
London, WC2A 1HN.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1976.  
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from  
which copies may be obtained.